United Journal of Drug Development and Industrial Pharmacy

PROSPECTIVE PROCESS VALIDATION OF LOPERAMIDE HYDROCHLORIDE B.P 2 MG TABLETS

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Article Information
Article Type: Research Article
Article Received: 22-05-2021
Article Accepted: 25-06-2021
Article Published: 30-06-2021
Vol:2, Issue:1

OPEN ACCESS

Keywords: Prospective Process validation; Loperamide Hydrochloride; Three consecutive process; Quality product.

INTRODUCTION

The The key to executing a successful validation is defining the exact process to be validated. Each parameter included in the manufacturing instructions must have a documented control space that has been established based on experimental or manufacturing data, as well as the quality of the starting materials and the capability of the operators, facility, equipment, and utilities. This requires an evaluation of historical data, deviations, and planned experiments during clinical batches (1-3).

To ensure that validation activities do not need to be repeated, the areas listed following in (**Figure:-1.1**: Process Validation flow chart) should be defined and qualified by a parallel path.

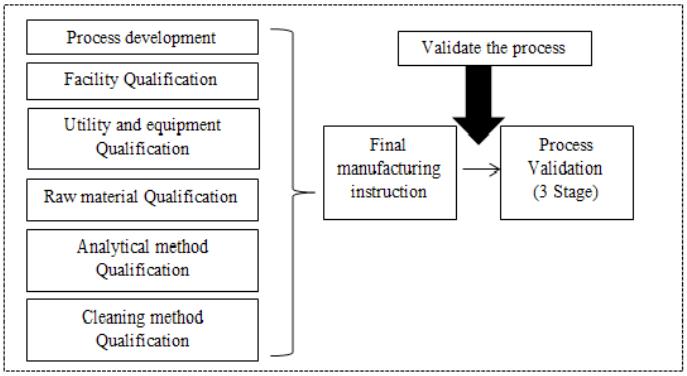

Figure:-1.1: Process Validation flow chart

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It involves series of activities taking place over the life cycle of product and process, which are regulatory, divided in to 3 stages (1, 4). (**Figure:-1.2:** Stages of Process validation)

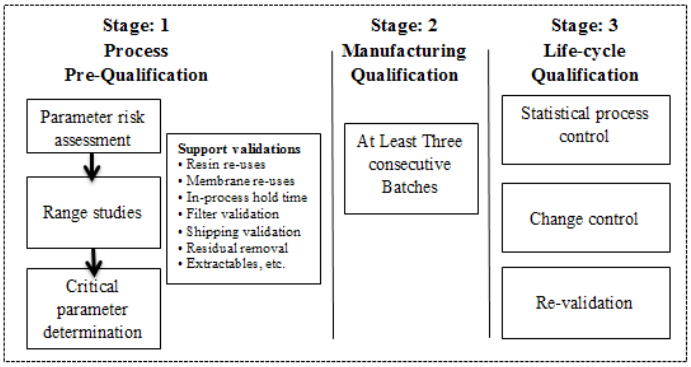
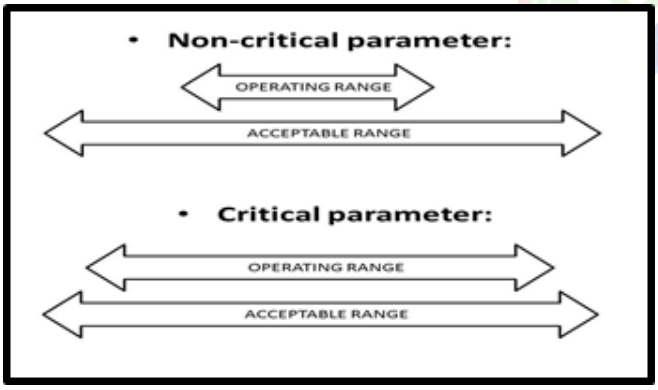


Figure:-1.1: Differences between Non-Critical and Critical parameters.

Figure:-1.2: Stages of Process validation.

Stage:-1: Pre-qualification activities.

Used to generate the list of critical process parameters in manufacturing qualification protocol (**Figure: 1.3** Differences between Non-Critical and Critical parameters). Process understanding needful to establish the design space and evaluation of process parameter on their range, it also involved the risk assessment and range finding studies. Each parameter is assessed for its potential to affect the applicable process controls or Quality attributes.



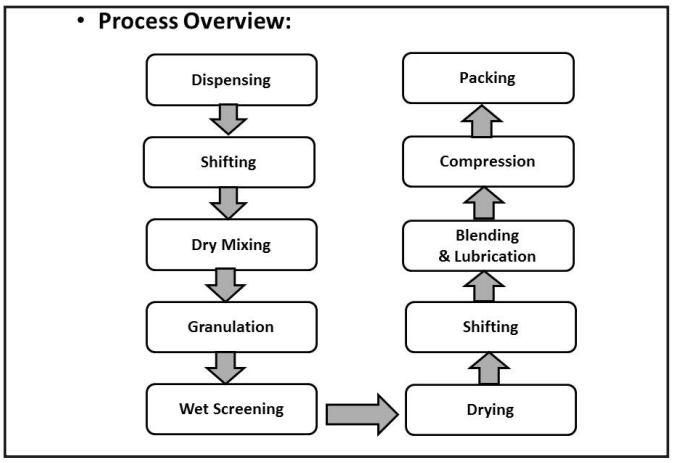
Stage:-2: Execution of the manufacturing qualification.

The Manufacturing process qualification is performed under a prospective protocol using the appropriate output and results from stage: 1 (critical parameter).

Stage:-3: Ongoing process monitoring though life cycle qualification and management of process changes.

Critical process parameter are monitored routinely during batch release and complied with specification data for annual reporting.

According to 2011 (USFDA) guideline [1], process validation is defined as "the collection and evaluation of data, from the process design stage throughout production, which establishes scientific evidence that a process is capable of consistently delivering quality products"



OBJECTIVE:

The object of this research is "Process Validation of Loperamide hydrochloride B.P 2 mg Tablets". This Prospective type of study is carried out in order to meet the current regulatory requirement and to prove with assurance that, the product meets predetermined specifications and quality attributes.

MATERIALS AND METHOD:

Granulation:

Loperamide Hydrochloride BP, Starch (Maize Starch), Lactose, Micro Crystalline Cellulose (MCCP), Sodium Methyl Paraben, Sodium Propyl Paraben, Purified Water.

Lubrication:

Magnesium Stearate, Talcum.

List of Equipments:

Vibro Sifter 30", Rapid Mixer Granulator 250 liter, Paste kettle 150 liter, Fluid Bed Dryer 120 kg, Multi Mill 75 kg/hr, Octagonal Blender 800 liter, Compression Machine 31 stations, Tablet De-Duster Tablet Inspection Belt, Strip Pack Machine.

List of Instruments:

Analytical Balance, Hardness Tester, Varneiar Caliper, Friabilator (USP), Disintegration (USP), LOD Instrument.

MANUFACTURING PROCESS: (**figure:-1.4** Manufacturing process on its individual step.)

Dispensing:

Weighing balances are leveled and calibrated.

Dispense all formulate accurate quantity material as efficiently, Quantity of API should be dispense using potency calculation formula and to be compensate with Quantity of Starch.

Dry Mixing:

Add Loperamide Hydrochloride BP, Starch (Maize Starch), Lactose, Micro Crystalline Cellulose (MCCP) previously weighed and sifted (Sieve No.40 #), sequentially in RMG and mix for 15 min at 100 RPM, after each 5 min interval withdraw (200 mg from 9 location (figure:-1.5

RMG- Rapid Mixer Granulator) + 1.8 gm Composite) samples by sampling rod , send the sample to Q.C department for analysis.

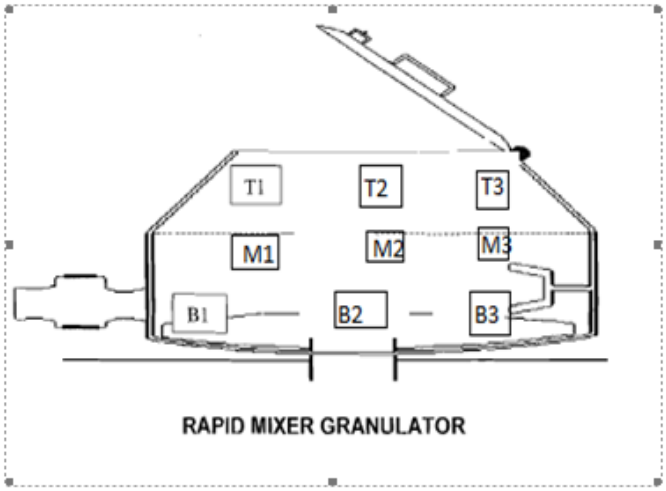


Figure:-1.5: RMG- Rapid Mixer Granulator.

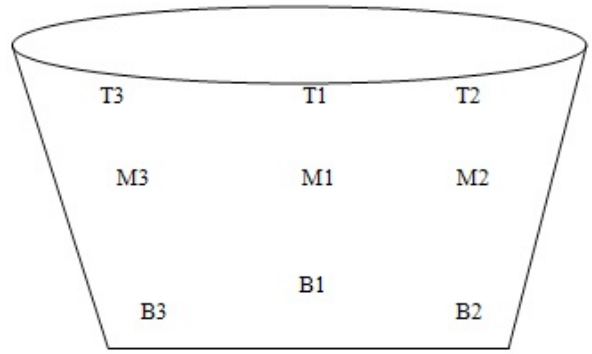


Figure:-1.6: FBD bowl.

Table No:- 01 PROCESS STEPS AND ITS CRITICAL PARAMETERS:

Steps	Independent Parameters	Dependent Parameters
Dry-Mixing	Blending time, RPM, Load Size, Order of addition.	Blend Uniformity.
Granulation	Mixing speeds, Amount of granulation fluid, Feed rate, Granulation time, Load.	Drug distribution, Water/solvent Content, Appearance (size).
Drying	Initial temperature, Outlet temperature, Drying temperature , Drying time.	Particle size distribution, Densities, Loss on drying, Assay for heat sensitive material.
Screening & Milling	Screen Size , Milling speed, Feed rate.	Particle size distribution , Tapped densities.
Blending & Lubrication	Blending time , Blender speed, Load size.	Particle size distribution , Tapped densities, Flow properties.
Compression	Compression rate, Granule feed rate, Pre compression force, Compression force.	Appearance , Weight variation , Hardness , Friability , Thickness , Moisture content , Disintegration , Dissolution , Assay , Dose uniformity.

Table: - 02 DRY MIXING RESULTS OF FIRST BATCH

Location	Assay Result (%)		
	5 min	10 min	15 min
T1: Top Left	99.76	96.28	97.92
T2 : Top Middle	100.72	97.73	94.73
T3 : Top Right	106.30	99.55	99.24
M1: Middle Left	107.22	99.66	98.40
M2: Middle Center	101.45	99.65	93.71
M3: Middle Right	100.54	98.87	100.08
B1:Bottom Left	98.17	101.02	99.72
B2:Bottom Center	99.75	98.70	98.54
B3:Bottom Right	98.25	99.73	95.99
Mean	101.35	99.02	97.59
% RSD	3.21	1.38	2.32

Note: Similar manner Data for second and third batches

Binding:

Take 27 liter Purified Water in clean Paste Kettle and heat up to 100°C. Add Sodium Methyl Paraben, Sodium Propyl Paraben and dissolve completely.

In a clean S.S. vessel take 5 liter purified water than add Starch (Maize Starch) slowly with continuous stirring. Further Pour the starch slurry in paste kettle with continuous stirring, finally all S.S vessel material Load in RMG and run the chopper during the mixing at slow speed till granulation. End point is reached to get required consistency of dough mass.

Drying:

Perform drying in FBD: Load the wet mass of respective lot in FBD bowl. Start drying the material in FBD by the cycle of required time interval at inlet temperature 60°c ± 5°c and outlet temperature 45° c ± 5° c. till water content of granules obtain NMT 5.0 % w/w at 105°c. After each drying cycle intervals collect 5 gm samples by sampling rod at 9 different locations (figure:-1.6 FBD bowl) from the FBD bowl for check LOD. After drying sift the granules through # 20 sieve using vibratory sifter and over size granules pass through Multi mill using 1.2 mm S.S. screen. After sifting and milling the granules load in Octagonal Blender.

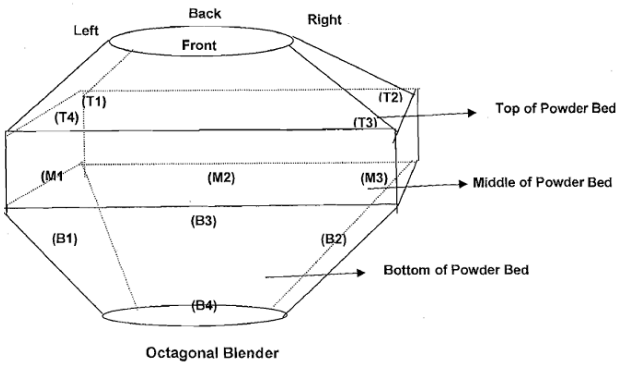


Figure:-1.7: Octagonal Blender

Table:-03 DRYING RESULTS OF FIRST BATCH, Concluded that in process challenged case the limit of drying complies after third cycle.

Table: - 03 DRYING RESULTS OF FIRST BATCH.

SAMPLE	LOD		
	FIRST CYCLE	SECOND CYCLE	THIRD CYCLE
TIME	15 min.	20 min.	15 min.
Acceptance Criteria: NMT 5.0 % w/w at 105 °C	13.64%	7.59%	4.91%

Note: Similar manner Data for second and third batches

Lubrication:

Add all lubricants (Talcum) previously weight and sifted (Sieve No. 60 #) except Magnesium Stearate & mix, add sifted Magnesium Stearate & continue mixing for 05 - 15 minutes & 35 RPM. After each 5 min interval withdraw (200 mg from 11 location (figure:-1.7 Octagonal Blender) + 75 gm Composite) samples by sampling rod, send the sample to Q.C department for analysis.

Table:-04 LUBRICATION RESULTS OF FIRST BATCH, Concluded that the granules blending and lubrication give require result after 10 min operation.

Table: - 04 LUBRICATION RESULTS OF FIRST BATCH

Location	Assay Result (%)		
	5 min	10 min	15 min
Top Left Back (T1)	100.39	98.56	98.48
Top Right Back (T2)	97.95	99.54	100.56
Top Right Front (T3)	96.30	100.05	95.62
Top Left Front (T4)	94.66	99.99	95.80
Middle Left Back (M1)	98.86	98.66	96.73
Middle Centre (M2)	95.60	98.89	101.00
Middle Right Back (M3)	97.00	98.30	98.34
Bottom Left Back (B1)	102.10	98.83	101.23
Bottom Right Back (B2)	98.98	99.48	98.39
Bottom Right Front (B3)	97.21	100.20	95.40
Bottom Left Front (B4)	97.30	100.25	97.77
Composite	102.23	98.90	97.99
Mean	**97.91**	**99.30**	**98.11**
% RSD	**2.25**	**0.69**	**2.03**

Note: Similar manner Data for second and third batches

Strip Packing:

Set the machine as per SOP, after setting the machine operate on selected temperature and speed, tests to be performed (for Strip-Table No.:- 06 STRIP PACKING PARAMETERS OF FIRST BATCH) Appearance, Sealing quality, Number of tablets in Strip, Horizontal Cutting and vertical cutting & Leak test during striping.

Table: - 06 STRIP PACKING PARAMETERS OF FIRST BATCH

Frequency	Sealing Temperature	Appearance Of Strip	Leak Test

Table: - 07 FINISHED PRODUCT ANALYSIS RESULTS.

Sr. No.	Parameter	Specification	Batch No.01	Batch No.02	Batch No.03
1	Appearance	White color standard concave round shaped uncoated tablet plane on both sides.	White color standard concave round shaped uncoated tablet plane on both sides.		
2	Weight of 20 Tablets (gm)	1.700 gm ± 2% (1.666 gm to 1.734 gm)	1.719 gm	1.699 gm	1.710 gm
3	Individual Weight Variation (mg)	85.00 mg ± 7.5 % (78.625 mg to 91.375 mg)	85.96 mg	85.56 mg	85.50 mg
4	Diameter (mm)	5.75 mm + 0.2 mm (5.55 mm to5.95 mm)	5.81 mm	5.82 mm	5.82 mm
5	Thickness (mm)	2.80 mm ± 0.2 mm (2.60 mm to3.00 mm)	2.85 mm	2.88 mm	2.85 mm
6	Hardness (Kg/cm2)	NLT 1.5 Kg/cm2	1.83 Kg/cm2	1.59 Kg/cm2	2.60 Kg/cm2
7	Friability	NMT 1.0 % w/w	0.29 % w/w	0.21 % w/w	0.15 % w/w
8	Disintegration time (min)	NMT 15 min	02 Min. 01 Sec.	01 Min. 51 Sec.	03 Min.15 Sec.
9	Identification test By HPLC	The principle peak in the chromatogram obtained with the test solution corresponds to the peak in the chromatogram obtained with the standard solution.	Complies	Complies	Complies
10	Uniformity of Dosage unit (Content uniformity)	85.00 % to 115.00% of labelled amount. RSD: NMT 5.0%	Mean: 98.58 % RSD: 0.73 %	Mean: 96.21 % RSD: 1.58 %	Mean: 97.10 % RSD: 1.11 %
11	Assay by HPLC	90.00 % to 110.00 % of labelled amount of Loperamide Hydrochloride	97.68 %	96.10 %	95.38 %

Initial	110 °c	complies	complies
Middle	110 °c	complies	complies
End	112 °c	complies	complies

Note: Similar manner Data for second and third batches

RESULT AND DISCUSSION:

The initial batch is experimented for various parameters. Base on that we challenged the process for its lower and higher space i.e. the worst case, and optimized process parameter which given us to Consistency Quality product and this range use to follow up routine manufacturing, Concurrent validation etc.

CONCLUSION:

By Performing the prospective type of process validation in tremendous manner and the overall review of results shows Homogeneity within a batch and consistency between batches and concluded that the goal of process validation is achieved and it full fill the both general and specific terms of CGMP regulation for finished pharmaceuticals.

ACKNOWLEDGEMENTS:

The authors are highly thankful to his friends, family and each member of Bhayani group who continuously support to me.

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